EXHIBIT A

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	**Master File No. 2:12-MD-02327** **MDL 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**
THIS DOCUMENT RELATES TO: ***Wave 2 Cases***	

TVT EXPERT REPORT OF JANET E. TOMEZSKO, M.D.

I. CREDENTIALS AND EXPERTISE

I am a board certified Female Pelvic Medicine Reconstructive surgeon, also known as a Urogynecologist, practicing at NorthShore University HealthSystem in the suburbs of Chicago, Illinois. I am board certified in Female Pelvic Medicine and Reconstructive Surgery as of 2013 and Obstetrics and Gynecology, 1998. I am licensed to practice medicine in Illinois and was previously licensed in Pennsylvania.

I also serve as an Assistant Professor in the Department of Obstetrics and Gynecology, University of Chicago, Pritzker School of Medicine. From 2001 to 2009 I held a similar academic appointment at Northwestern University Medical School. Prior to that I was a Clinical Assistant Professor at the University of Illinois at Chicago from 1998 to 2001. In these roles I have educated and trained medical students, residents and fellows in gynecology and female pelvic reconstructive surgery, including urogynecolcogy. I have taught fellows and residents how to assess and counsel patients on various conditions including incontinence and have also taught stress urinary incontinence surgery using the Ethicon TVT and TVT-O devices. I have also taught fellows, residents and students the basic elemental surgical risks of

incontinence surgeries such as the Burch colposuspension, pubovaginal slings and midurethral slings as discussed later. Knowledge of these risks is part of the core competencies of the gynecologic surgeon and female pelvic medicine and reconstructive surgeon and is also tested in our board certification process.

I received my Doctor of Medicine from Hahnemann University/Drexel University School of Medicine in 1991 and was elected into Alpha Omega Alpha. From 1991 to 1995 I did an Obstetrics and Gynecology residency at Lehigh Valley Hospital and served as Chief Resident. During my residency we performed various stress urinary incontinence surgeries including the Burch colposuspension and suburethral/pubovaginal sling with autologous tissue and graft material and for prolapse repair we performed various native tissue repairs and abdominal sacral colpopexies, first with Goretex and then with Mersilene mesh. I then did a fellowship in Urogynecology at Northwestern University from 1995 to 1997 performing the various incontinence and prolapse surgeries.

After finishing my fellowship, I entered an academic and clinical practice that led to my role as Director and then Chief of the Section of Urogynecology & Female Pelvic Surgery at Northwestern University Medical School. I have a

busy clinical practice, and perform about 150-200 female reconstructive procedures a year. Over my 20-year career I have performed over a thousand gynecologic and female pelvic reconstructive surgeries. I was trained and have performed the full complement of abdominal and vaginal surgeries. I have used biologic and synthetic grafts as well as native tissue repairs for incontinence and prolapse surgery.

I was trained on and have performed stress incontinence surgery utilizing the Gynecare retropubic TVT procedure since 1999. I have performed over 1,500 retropubic TVTs over the past 15 years. I have also performed other mid-urethral sling procedures including the transobturator approach (TVT-O).

I am a Fellow of ACOG and a member of AUGS and SUFU, formerly a member of IUGA. I am a recognized expert in the field of Female Pelvic Medicine and Reconstructive Surgery/Urogynecology and have published several scientific articles and given many lectures in this. My publications and presentations include the surgical treatment of pelvic organ prolapse and stress urinary incontinence including the use of TVT. These studies have been presented at both national and international scientific meetings.

For additional information please refer to my attached Curriculum Vitae.

II. MATERIALS REVIEWED

I have regularly researched and reviewed the medical literature concerning the treatment of Stress Urinary Incontinence (SUI) for decades. I have also reviewed the Ethicon TVT Instructions for Use, Professional Education materials made available to pelvic surgeons who may choose to use TVT, TVT surgical videos, the TVT Surgeons Resource Monograph, and other Ethicon documents. I have reviewed Professional society analyses, systematic reviews, guidance and statements. A list of these materials and those that I may use at trial are attached to this report. I have also reviewed the Plaintiffs' expert reports and the materials cited by Plaintiffs' experts.

III. FEES AND PRIOR TESTIMONY

My fees for serving as an expert in this matter are: $400 per hour for review, report drafting and meetings, $3,500 per day for deposition and $5,000 per day for trial testimony. I have not given expert deposition testimony in the prior four years.

IV. OPINIONS

Urinary Incontinence

Urinary incontinence is a prevalent and significant problem for women of all ages. Urinary incontinence may interfere with daily activities of life, work, physical health, functional abilities as well as emotional health of the women affected. The prevalence of urinary incontinence in a large general population study estimated 15.7% of women experience urinary incontinence, over the age of 20. Over the age of 60, 23.3-31.7% of women are affected by urinary incontinence (Nygaard, JAMA, 2008). Metanalysis by Hampel, Urology 1997, revealed that 49% of women with urinary incontinence had stress type. A study of women with stress urinary incontinence (SUI) symptoms showed three fourths were bothered by their symptoms, with 29% being extremely bothered (Fultz, AJOG, 2003). The studies find that these symptoms result in problems that are physical, psychosocial, economic and may result in psychological distress, social isolation, loneliness, falls, and negative financial impact. Quality-of-life surveys show significant disruption and quality of life due to these urinary symptoms. Risk factors for stress urinary incontinence include age, pregnancy and childbirth, obesity, chronic coughing or chronic physical exertion, menopausal status, diabetes and

genetic predisposition. An estimated 13.6% of American women will elect to undergo surgical treatment of stress urinary incontinence during their lifetimes (Lavelle, OBGYN Clinic NA, 2016).

As defined by the International Continence Society (ICS) Joint Report on the Terminology for Female Pelvic Disorders 2010, urinary incontinence is the complaint of involuntary loss of urine. There are several different types of symptoms urinary incontinence that affect patients.

Stress urinary incontinence is defined as involuntary loss of urine on effort or physical exertion (sporting events) or sneezing or coughing.

Urgency urinary incontinence is defined as the complaint of involuntary loss of urine associated with urgency.

Mixed urinary incontinence is the complaint of involuntary urine loss associated with urgency and also with effort or physical exertion or on sneezing or coughing.

Other symptoms of urinary incontinence include insensible urinary incontinence which is the complaint of urinary continents when the woman is unaware of how it occurs. There is also continuous urinary incontinence with

the symptom of continuous involuntary loss of urine. Coital urinary incontinence is the complaint of urinary incontinence during coitus.

These symptoms of urinary incontinence upon medical evaluation can be ascertained to be due to definitive causes of bladder and urethra dysfunction. The true different causes of the types of urinary incontinence result in different treatments to alleviate the symptoms.

Upon undergoing medical evaluation including urodynamic testing, which evaluate the function of the bladder and urethra, we are able to ascertain causes of urinary incontinence.

Urodynamic stress incontinence is defined as the diagnosis by symptom, sign, and urodynamic investigations involve the finding of involuntary leakage during filling cystometry associated with increased intra-abdominal pressure.

Detrusor overactivity is defined as symptoms and Urodynamic investigation that finds involuntary muscle contraction during filling cystometry.

Cause of SUI

The urethra continence mechanism includes multiple components. The urethra maintains internal tone through the smooth muscle wall and the skeletal muscle of the urethral sphincter. The mucosal lining of the urethra allows increased coaptation and continence pressure, which is dependent on healthy urethral mucosal lining and healthy blood supply to the lining. Under passive conditions mechanical compression of the urethra is induced by supportive pubourethral ligaments, fascia attached to the levator ani muscles, and the surrounding tone of the levator ani muscles. (Koike, IJUrology, 2013)

Under active condition the urethral closure mechanism relies upon increases tone of the urethral sphincter, skeletal muscle components, and support of urethra by the periurethral ligaments and levator ani muscles.

Loss of these functions can contribute to SUI. Weakened periurethral ligamentous support and pelvic floor muscles defects may result from childbirth, obesity, and chronic increased abdominal pressure such as obesity, chronic cough, constipation and heavy lifting. These deficits often result in a loss of urethral support as seen on examination with the urethra showing deviation from normal support (approximately angle of -30 to 0 degrees) with valsalva to hypermobility with an angle of greater than 30 degrees.

Other contributing components include loss of elasticity of the urethral walls preventing coaptation if the urethral mucosa. This can be contributed to by loss of estrogen, menopausal, status, as well as loss of collagen. Neurological deficits may contribute also. A more severe form of loss of the internal urethral continence mechanism results in a "drain pipe urethra" known as Intrinsic Sphincteric Deficiency (ISD). ISD is defined as low leak point pressure measured on urodynamic testing, most commonly defined as under 60 cm of water. ISD implies that the urethral coaptation mechanism does not close even with at rest.

Nonsurgical treatment of SUI

Nonsurgical treatment options for stress urinary incontinence have been a mainstay of therapy and include effective options for patients without the risks of surgery. Initially interventions implemented behavioral and lifestyle modifications. These treatment options may include bladder retraining, fluid management, and weight loss. Bladder retraining involves instructing the patient on methods to improve bladder control using mind over bladder educational techniques. Fluid management including reduction of caffeine and carbonation intake, improving water intake, and being conscious of when

fluids are consumed have proven helpful. Weight-loss of only 10% of body weight has been shown to improve symptoms.

Significant improvement in symptoms can be obtained through strengthening the pelvic floor muscles that support and surround the urethra and bladder. These exercises can be performed by the patients through standard pelvic floor muscle education. Biofeedback can improve results and can be implemented with many different options, including vaginal cones, home or office biofeedback devices. More effective training can result from the patient being under treatment by a pelvic floor physical therapist who specializes in the utilization of techniques to prove the strength of the pelvic floor or levator muscles. These treatments may include biofeedback, functional electrical stimulation of the pelvic floor muscles, as well as other techniques augment the treatment, to provide more efficacious strengthening of the pelvic floor muscles.

Vaginal inserts, incontinence pessaries, have also been developed to treat stress urinary incontinence. These inserts are designed to support the urethra and provide improved closure of the urethral continence mechanism during activity, exertion, and coughing and sneezing to prevent the urinary leakage. Pessaries can be very effective for the prevention of stress and SUI

symptoms. The device requires an appropriate fit in the vagina which may not always be possible. Also pessaries require long-term maintenance with removal and cleaning which may become bothersome to the patient. Recently and over the counter device has been developed to perform the same function. This allows patients to attempt self-treatment for the vaginal insert prior to seeking medical care. Discharge, bleeding, erosion and other risks are attendant to pessary use.

In the past other devices were also utilized to treat SUI include the urethral plug and a urethral patch. The urethral plug required the patient to insert a device into the urethra which would allow occlusion of the urethra during activities to prevent SUI. The urethral patch covered the urethral meatus to prevent urinary leakage. Both devices needed to be removed to void and replaced after the void.

Urethral injection therapy has also been utilized in cases of SUI. This is an invasive option requiring injection of materials such as autologous fat, collagen (no longer available), calcium hydroxalate (Coaptite), polydimethylsiloxane (Macroplastique), carbon coated graphite beads (Durasphere) to allow the internal urethral closure mechanism to have more coaptation and improve continence. These injections do require repeat

injection and also carry similar risks of surgery including UTI, infection and foreign body complications sometimes requiring surgical intervention.

Injection of autologous harvested stem cells into the urethal wall is currently under evaluation. The goal is to improve the continence mechanism by rebuilding the muscular tone of the urethra. Our practice participates in these studies.

Treatment of SUI before TVT

Surgical options for the treatment of SUI have evolved over the last several decades. In the early 1900's the surgical management of SUI primarily involved the Kelly-Kennedy plication of suburethral tissue. This is a native tissue repair often performed at the time of anterior colporrhaphy. This was the standard of care until the 1980's when the surgical options for SUI became more diverse. It is no longer recommended by the pertinent societies due to lack of effectiveness.

Native tissue sling operations also came into use in the early 1900's. They were performed with gracilicus muscle flaps, pyramidalis muscles, developing into procedures incorporating fascia of different types. Rectus

fascia and tensor fascia lata were utilized, with eventually the addition of cadaveric fascia. Eventually the fixation point of the pubovaginal slings became the rectus fascia to add an active component to the sling function allowing active compression of the urethra as the rectus muscle contracted. These are more morbid procedures with harvest complications, long term nerve and wound complications, higher rates of voiding dysfunction and retention due to obstruction.

The next major change in incontinence procedures were the development of the retropubic procedures in the late 1950 early 1960's. These invasive procedures allowed better support of the urethra in more anatomic position and function and these procedures, particularly the Burch procedure remain in use today.

However, these procedures have significant risks and morbidity including voiding dysfunction, wound complications and infection due to open or laparoscopic approach and fascia harvesting for slings, long term de novo detrusor instability/OAB/UI, pain dyspareunia and groin pain, prolapse, high rates of UTI, and their efficacy falls off with longer term follow up. (Galloway, Br J Urology, 1987; Eriksen, Actn Obstet Gynnecol Scand, 1990; Alcalay, BrJ Obsret Gynaecol, 1995; Chaliha, Br J Obstet Gynaecol, 1999;

Demirci, Gynecol Obstet Invest, 2001; Kjolhede, Acta Obstet Gynecol Scand, 2005; Albo, NEJM, 2007; Richter, J Urology, 2012; Brubaker, J Urology, 2012)

The need for minimally invasive procedures was identified as early as the late 1950's through the 1970's with the introduction of multiple variations of the minimally invasive needle suspensions. These procedures were also designed to resupport the urethra by returning the urethra to a stabilized state. The procedures included the Pereyra, Modified Pereyra, Stamey, Raz, Gittes, Leach Bone fixation, and Vesica procedure. An AUA panel in 1997 reviewed the literature on the safety and efficacy of these procedures, and the long-term overall success was about 67%, which was significantly lower than the rates for Burch and slings, and the procedures were not considered adequate treatment. These procedures also held significant rates of morbidity with 5% rate of bladder injury, 3% urethral injury, 3-5% bleeding, 8-16% nerve entrapment, 10% postoperative pain, 7% wound infections and 33-80 % late failure (suture pull through or anchoring failure). (Bodell, UrolClinicsofNA, 2002)

A prospective randomized study of Kelly plication, modified Pereyra needle suspension, and Burch urethropexy procedure was performed by Bergman

with 5 year follow-up. The results showed superiority of the Burch procedure over the other procedures. Success at 5 years was Kelly plication 37%, Pereyra 43%, and Burch 82% (Bergman, AJOG, 1995)

As noted by the first systematic review on the subject, the evidence base was significantly lacking for all of these procedures, some of which had been in use for many decades and counseling on risks was haphazard due to significant deficiencies in the medical literature, namely the lack of reliable data on the frequency of complications rendering their safety unclear. (Black & Downs, Br J Urology, 1996) As shown later, TVT ushered in a paradigm change with scores of studies and RCTs done each year and has the largest evidence base of all incontinence procedures.

Artificial urinary sphincters have also been utilized since the early 1970's. The artificial sphincter is utilized in only the most severe cases of SUI and carries an extremely high morbidity. Success by patient-reported pad use and various questionnaires, was achieved in 61–100% of cases (no pad or one pad per day). A pooled analysis showed that infection or erosion occurred in 8.5% of cases (3.3–27.8%), mechanical failure in 6.2% of cases (2.0–13.8%). Reoperation rate was 26.0% (14.8–44.8%). (Van der Aa, European Urology, 2013)

Design and Development of TVT

The earliest prototypes for the TVT device critically evaluated the use of a variety of these synthetic materials, such as Mersilene and Gortex before the Prolene mesh was found to be best (Petros 2015; Ulmsten et al, 1996). These authors also reported that these materials (Gore-Tex, Teflon, Mersilene) were associated with significant inflammatory reaction in paraurethral tissues and caused a significant amount of tape rejection. (Falconer et al, 2001).

As noted by AUGS and SUFU: Polypropylene material has been considered safe and effective as a surgical implant for over five decades, and has been used in a majority of surgical specialties including general surgery, cardiovascular surgery, transplant surgery, ophthalmology, otolaryngology, gynecology and urology. As an isolated thread, Prolene polypropylene is used widely as a permanent and durable surgical suture. As a knitted material, polypropylene mesh is the consensus graft material in a number of areas in the human body.

Specifically, type 1 mesh is universally recognized as possessing the highest biocompatibility with the least propensity for infection. (Ford Cochrane Review 2015) TVT macroporous lightweight monofilament mesh has been

shown to be most tolerated, safe and efficacious (AUGS SUFU Position Statement 2015). The FDA and AUGS/SUFU, as well as the AUA, ACOG, and IUGA, have specifically determined that the safety and effectiveness of polypropylene multi incision midurethral slings is well established and that data is most often based upon the TVT device. (FDA Considerations about surgical mesh for SUI 2013; AUGS-SUFU Statement 2014; AUA Position Statement on the Use of Vaginal Mesh for the Surgical Treatment of Stress Urinary Incontinence Oct. 2013; IUGA Position Statement on Mid-Urethral Slings for Stress Urinary Incontinence July 2014; ACOG Practice Bulletin 2015).

The detailed design of TVT is catalogued by Dr. Peter Petros in the publication attendant to the Ulf Ulmsten Memorial Lecture in 2014 as further described below. (Petros, IUJ, 2015). Notably, TVT is so revolutionary that a significant yearly lecture is named after Dr. Ulmsten in light of the incredible positive utility that TVT has brought to the treatment of female stress urinary incontinence. TVT was designed over many years by pelvic surgeons like myself. We understand continence pathophysiology and the state of the art of continence repair. The process of developing the TVT began when pelvic surgeons evaluated the shortcomings of the then-existing continence

procedures like the Burch and pubovaginal sling. From beginning observations and hypotheses to animal testing and then human testing, the development of the TVT sling marked a significant shift in the understanding of pathophysiology of SUI.

Animal studies began in 1987 at the Royal Perth Hospital animal laboratory. The purpose of the animal studies was to determine whether the surgical methodology of implanting a tape to restore the PUL was a safe and effective procedure that could be used for humans. The animal selected to test this procedure on was a large dog. The tape was implanted in the dogs in a manner where two ends of the tape would stay loose in the vaginal cavity for 6-12 weeks. Observations following the implantation in the dogs indicated positive reactions including normal white cell counts, low inflammatory response in the tissues, and that the dogs remained afebrile. The lack of pathogenic bacterial growth affirmed that the macrophages in the interstices of the tape illustrated that the tape successfully prevented bacteria. Additionally, a collagenous cylinder formed around the tape. The only negative effect observed was a sticky vaginal discharge. Based on these observations, it was determined that the procedure of creating an artificial collagenous neoligament had been successful.

In 1988 and 1999, following the success of the animal studies, 30 women diagnosed with stress incontinence underwent the prototype TVT operation. Out of the 30 women, 25 were reported to have mixed incontinence and 5 had only urinary stress incontinence. This operation was performed by using the tunneler instrument to insert the Mersilene tape into the vagina in the location of the midurethra. The tube was lowered into patients with the use of interrupted sutures. Once the sling was lowered toward the lower end of the symphysis, obstructed urine flow returned to normal. Following this procedure, all thirty patients remained continent for the 6 weeks the tape was implanted. The 25 women with mixed incontinence were cured of both stress and urge incontinence. After removal of the tape, 50% of patients reported both recurrence of stress incontinence and urge incontinence within 2 weeks.

Following the human studies, several issues stood out that eventually led to the evolution of the integral theory. The first anomaly addressed whether stress and urge incontinence have the same origin since they were cured and would recur simultaneously? Secondly, since urge incontinence had been surgically cured, what was the mechanism for the cure? The third anomaly addressed the lack of bladder neck elevation, despite the position of the balloon in regards to the lower end of the symphysis, invalidated Enhorning's

pressure equalization theory. Lastly, when the patient was asked to strain after the tape was grasped with a hemostat, three directional vector forces, forward, backward and downward became evident, triggering the question of what was the role of the directional forces in urgency control and urethral closure? None of these issues could be explained with existing concepts, leading to the creation of a new theory.

Petros and Ulmsten published "The Integral Theory" in 1990. This theory described the critical interaction between the pubourethral ligaments supporting the mid-urethra, the levator ani muscles, and the elastic anterior vaginal wall. The focus became directed towards a surgery that provided dynamic support at the mid-urethra. This replaced the approach of providing static support to the bladder neck. The Integral Theory introduced a stable platform of support, against which the mid-urethra could be compressed during increased intra-abdominal stress.

Additionally, there goal was to determine a surgical procedure that did not require a major incision, would require a shorter recovery time, could be done under local anesthesia, and would be considered "minimally invasive." The 2-year outcomes of a new sling implanted in 75 women, called the intravaginal slingplasty (IVS) were published by Ulmsten and others in 1996.

The IVS was a synthetic, polypropylene sling that was inserted through a small vaginal incision into the retropubic space using metal trocars. The mesh sling was placed using a completely tension-free manner. The procedure took approximately 22 minutes and was done under local anesthesia. There was no static elevation or support of the urethra when using this method. A follow-up after 2 years revealed a cure rate of 84% with no reported cases involving major post-operative complications or mesh erosion. (Ulmsten 1996). Later clinical trials demonstrated the appropriateness of the TVT procedure in treating the entire spectrum of SUI disorders, including its efficacy in treating primary stress incontinence, recurrent stress incontinence, mixed urinary incontinence and intrinsic sphincter deficiency, all with consistently excellent results (Rezapour & Ulmsten, 2001; Rezapour et al, 2001; Nilsson et al, 2001; Kuuva et al, 2002 registry.)

Safety, Efficacy, Utility and Desirability of TVT

Based on extensive and thorough scientific investigation, the TVT has become the new gold standard procedure for the treatment of primary and recurrent SUI. Dating as early as 2002, an IUGA survey showed TVT was the procedure of choice for stress incontinence (48,8%), followed by Burch colposuspension (44%) and autologous fascial slings (3.8%) (Davila GW, Int

Urogyn J, 2002). The TVT sling is the most studied procedure in all of gynecology. There are over 2000 publications and studies in the scientific literature involving thousands of women, including the highest level I scientific evidence (Ogah, 2009). The TVT has been endorsed, based on its voluminous and long term data showing efficacy, utility, desirability and safety, by the major female pelvic reconstruction organizations in the United States such as ACOG, AUA, AUGS, IUGA, SUFU, and SGS, as well as abroad such as IUGA, NICE, ICS and the European Association of Urology.

Comparative studies addressing different types of retropubic slings found the TVT to be superior. The TVT had significantly better results than the intravaginal slingplasty (IVS OR 0.47, p=0.007) (Ford, 2015; Meschia 2006; Ulmsten 1996). The TVT was also found to be more decidedly more efficacious than the top-down retropubic approach. (SPARC OR 0.53) (Novara, 2007; Ogah, 2011). Ogah reported that the minimally invasive TVT had fewer bladder perforations (4.7% vs 8.5%, RR 0.55, 95% CI 0.31-0.98) and tape erosions (0.7% vs 3.5%, RR 0.27, 95% CI 0.08-0.95) than the top-down approach. It also reported a favorable profile comparative to the Burch – both open and laparoscopic, and the pubovaginal sling.

All operations, including mid-urethral slings, are associated with potential risk. The potential risks associated with the TVT procedure are risks present with all anti-incontinence procedures (Schimpf, 2014; Chahila 1999, FDA 2013 Considerations for SUI Mesh). Surgeons performing any incontinence procedure require knowledge of abdominal, retropubic, and vaginal anatomy in addition to comprehensive knowledge of bladder and urethral physiology. Surgeons obtain this knowledge during medical school, residency, post-graduate training and from personal experience. Industry sponsored publications such as IFUs are required by the FDA, and these documents should be used to supplement the surgeon's knowledge. However, they do not serve as the single reliable source of information for implanting surgeons. In addition to learning how to perform the TVT procedure, surgeons are required to fully understand potential complications be prepared to manage such complications as they arise. These risks are learned in surgical textbooks and medical literature. Additionally, they are tested during surgical training and included as questions on major board certification examinations. Risks are also discussed during continuing professional education such as workshops and seminars at regional and national meetings. All of the risks associated with the TVT procedure have long been reported in the medical literature and it is fully expected that surgeon users are familiar with all of

these risks, both as they relate to any pelvic surgical procedure as well as the TVT procedure. These risks are thus commonly known and should be known to pelvic surgeons who would employ the device. The only unique risk of TVT is mesh exposure and erosion and it is warned of in the IFU, Professional Education, hundreds if not thousands of papers in the medical literature, is taught and discussed in medical residencies and fellowships and CMEs, discussed in medical society papers and at conferences, discussed in the FDA alerts, and a myriad of other venues and vehicles like Grand Rounds, etc. I have reviewed the TVT IFU and find that it presents the risks of the device which would not otherwise be known by pelvic surgeons.

Cochrane Reviews, Systematic Reviews and Meta-analyses

A Cochrane Review, which is an independent reviewing body, published its Level 1 systematic review and meta-analysis comparing minimally invasive midurethral slings to traditional suburethral slings. The Ogah 2009 Cochrane Review reported results from 62 trials involving 7,101 patients. The results demonstrated that minimally invasive midurethral synthetic slings, such as TVT, were as effective as traditional suburethral slings. The data also confirmed that midurethral slings like the TVT had additional benefits including shorter operating time, less post-operative voiding dysfunction, and

less de novo urgency symptoms (Ogah, Cochrane Rev, 2009). The study also found synthetic midurethral slings to be as effective as open Burch procedures, but with fewer perioperative complications, less post-operative voiding dysfunction, and shorter operative time and hospital stay. The TVT had more bladder perforations.

An updated Cochrane Review affirms the efficacy, safety and utility of TVT for the treatment of SUI (Ford, Cochrane Review, 2015). The 2015 Review included 81 trials that evaluated 12,113 women for up to a five year follow-up. The overall rate of adverse events was consistently low. In fact, the Review noted that "overall reports rates of tape-related complications are low, such as erosion of the tape into the vagina is at about 2% for both routes of tape insertion," and "the reported occurrence of problems with sexual intercourse including pain was low, and leakage of urine during intercourse improved following insertion of these tapes." The Review found that that "Mid-urethral sling operations have been the most extensively researched surgical treatment for SUI in women and have a good safety profile," and that "Mid-urethral sling operations are a recognized minimally invasive surgical procedure for SUI." When reference is made to Mid-urethral slings they are relying upon the vast amount of data for the TVT device.

A systematic review and meta-analysis was conducted in 2014 by the Society of Gynecologic Surgeons (SGS) evaluating traditional pubovaginal versus mid-urethral slings. The Review revealed that subjective cure rates were over 50% lower in the traditional sling group (OR 0.40, 95% CI 0.18-0.85). Based on these results, SGS recommended preferential use of mid-urethral slings (Schimpf, 2014) for SUI.

Urinary urgency, frequency and urgency urinary incontinence are common in women. They occur and up to 40% of women. Although TVT is not indicated to treat urge incontinence, the literature that shows that upwards of 65% of patients with UI and urgency may have improvement following TVT.

Bladder erosion is a long known, warned of and reported rare potential complication following TVT with rates less than 1%. (Ford 2015 Cochrane Review, Analyses 1.23 and 4.15; Novara 2008 Table 6) Bladder erosions are also a risk of non-mesh incontinence surgeries such as the autologous pubovaginal sling. (Clemens JQ, DeLancey JO, Faerber GJ, Westney OL, Mcguire EJ. Urinary tract erosions after synthetic pubovaginal slings: diagnosis and management strategy. Urology 2000; 56:589-94.)

Wound complications and infections occur at lower rates with TVT than with the Burch and autologous slings. (Schimpf, AJOG, 2014; Albo, NEJM, 2007; Albo, JUrology, 2012) Erosions can also occur with these other procedures as well as noted above. (Schimpf, AJOG, 2014; Athanasopoulos, Urology, 2011; Walter, Am J Obstet Gynecol, 2001).

Mesh exposure is a long known, warned of and uncommon potential complication following TVT with rates in the 1-2% range based on the most reliable data. (Ford 2015 Cochrane Review: 2.1%; Schimpf 2014 meta-analysis: 1.4%; Tomaselli 2015 meta-analysis: 2.1%; Ogah 2009 Cochrane Review: monofilament tapes 1.3%; Novara 2008 meta-analysis, table 6: 1.1% vaginal erosion; 2000 TVT Surgeons Resource Monograph).

The risk of future need for excision is very low at <1% to about 2%. (Unger 2015: 19 of 3,307 women underwent sling revision due to mesh erosion, 0.6%; Laurikainen 2014 RCT: no women required revision for exposure; Schimpf 2014 meta-analysis: 1.9% return to OR for mesh exposure; Svenningsen 2013 10 year prospective study: 3 excisions due to mesh exposure, 0.6%; Jonsson Funk 2013 database study: 9 year risk of excision 2.5%; Serati 2012 10 year prospective TVT study: no women required revision for exposure; Nguyen 2012 Kaiser Permanente database study: 0.9%

excision due to mesh exposure) Notably, wound complications are a risk of other surgical procedures to treat SUI as well. (Schimpf 2014 metaananlysis)

Dyspareunia is very common in women. (Jamieson 1996: 46% prevalence of dyspareunia in a consecutively sampled group of women presenting to two Obgyn and 3 family practices with 45% experiencing pain for more than a year, 48% experiencing sexual dysfunction, and 25% reporting pain both during and after intercourse) Dyspareunia is a well-known and reported risk following incontinence surgery and vaginal surgery, and the risk of dyspareunia with TVT is lower than that of non-mesh SUI surgeries. (Schimpf 2014 metaananlysis; AUA 2012 metaanalysis and SUI Guidelines).

The most recent systematic review of long term studies shows that persistent or chronic pain -- defined as pain persisting beyond the perioperative period or reported at the last follow-up visit -- was reported by 13 of 3,974 Retropubic TVT patients (Tommaselli 2015 metaanalysis) This translates to a rate of 0.3%.

Other high level data show a very low rate of dyspareunia and surgery due to pain complaints. (Unger 2015: 7 of 3,307 women underwent sling revision due to vaginal pain/dyspareunia, 0.2%; Schimpf 2014 meta-analysis: 0%

TVT; Laurikainen 2014 RCT: no women in TVT arm required revision for dyspareunia; Svenningsen 2013 10 year prospective study: 0%; Serati 2012 10 year prospective TVT study: no women had de novo dyspareunia; Nguyen 2012 Kaiser Permanente database study: 1 out of 2,339 retropubic TVT patients (0.02%) had an excision for pain)

Urinary tract infections are very common in women and following more invasive incontinence procedures like the Burch and pubovaginal sling. (Foxman B & Brown P: Epidemiology of urinary tract infections: transmission and risk factors, incidence, and costs. Infect Dis Clin North Am 2003; 17: 227-41; Dielubanza E & Schaeffer A. Urinary tract infections in women. Med Clin N Am 2011; 95:27–41) Recurrent UTI is a common finding in postmenopausal women with rates reaching between 25 and 50% and can be due to many factors (Dielubanza E & Schaeffer A. Urinary tract infections in women. Med Clin N Am 2011; 95:27–41) They are also a known risk of vaginal surgery and SUI and POP surgery without mesh. The risk of UTIs is lower with TVT than with the Burch colposuspension or the autologous pubovaginal sling. For example, the rate of UTI was 32% with the Burch procedure and 48% following fascial sling procedure in the two year SISTER trial results. (Albo 2007) The rate of UTI was 17.4% for TVT

in the TOMUS trial. (Albo 2012) UTIs are also common with menopause alone as well as vaginal atrophy. The most common cause is postmenopausal atrophic vaginitis allowing the patient to be prone to UTI. (Dielubanza E & Schaeffer A. 2011) Incomplete bladder emptying can also contribute to urinary tract infections, which is one of the reasons why there are elevated rates following Burch and autologous slings. (Ogah, Cochrane Review, 2011, Albo, NEJM, 2007)

These beneficial attributes and utility have led to the adoption of midurethral slings and specifically TVT as the preferred option for the treatment of stress incontinence by urologists and urogynecologists (AUA Position Statement, 2013; ACOG Practice Bulletin, 2015; Chughtai et al, 2013; Nager et al, 2012; ICS Stress Urinary Incontinence Fact Sheet 2013; Clemons et al, 2013; Rogo-Gupta et al, 2013; Wu et al, 2014).

Plaintiffs' claims:

Weight and Pore Size

The effective porosity theory adopted by plaintiffs' experts is not an accepted by experts in the field of gynecology, urogynecology, or urology. The theory

advanced by plaintiffs' experts is also not supported by the SUI literature. Literature reporting the outcomes of TVT procedures reflects that the pore size and weight of TVT mesh is appropriate and acceptable for treating stress incontinence. The Prolene TVT is as an Amid Type I macroporous mesh, which is the generally accepted classification for biomaterials. Type I mesh is monofilament with a pore size greater than 75 microns. It is often described as large pore, lightweight mesh. (AUGS/SUFU 2014 Position Statement). The large pore size facilitates infiltration of the mesh by blood vessels, macrophages and fibroblasts. The pore size, mesh construction, and weight assist in supporting the midurethra and allowing for tissue ingrowth. Complications do not occur at an increased frequency because of the pore size or weight of the mesh. Any claims by the plaintiffs' experts' alleging that changes in pore size and weight would improve clinical efficiency by reducing complications and improving patient outcomes are unfounded and not supported by clinical literature or RCTs. Studies that evaluate other meshes with larger pores and lighter weight than TVT mesh, such as Vypro, have not shown a decrease in complications. A study publishing the results regarding pelvic floor repairs for prolapse where Vypro was used were poor in conjunction with a high rate of mesh erosions. (Dennis, ICS/IUGA, 2004). Additionally, I am aware that Ethicon requested feedback from pelvic floor

surgeons regarding interest in a lightly weight, larger pore mesh for TVT, and the responses did not suggest surgeons wanted any changes in the TVT mesh. (Eth.Mesh.06377498). This theory has not been substantiated in the context of the TVT sling by reliable data. And thus, any claim that such a warning is needed in the TVT IFU is without merit as this is not a risk.

Mechanical versus Laser Cut

An additional claim has been made suggests mechanically cut mesh is inferior or causes complications as compared to laser cut mesh. Plaintiffs' experts claim that if mesh is mechanically cut as compared to being cut with a laser, small particles can adhere to the mesh, inducing an inflammatory and cytotoxic host response. The TVT sling exclusively used mechanically cut mesh between the years of 1998 to 2007. Despite the introduction of laser cut mesh in 2007, Ethicon continued to make and sell mechanically cut mesh as well. Ethicon still sells both mechanically cut and laser cut TVT in order to satisfy surgeon preferences. The edges of mechanically cut mesh are not sharp and do not cut into tissue and cause complications. I am aware of literature in which the authors hypothesized about differences in the cut of the sling attributing to complication rates, but this is nothing more than speculation. In a 2011 comparative study evaluating TVTTM-O

(mechanically cut) and TVTTM-Secur (laser cut), the authors speculated that higher rates of dyspareunia in the TVTTM-Secur group may be explained "in part by the rigidity and reduced flexibility of the synthetic polypropylene implant because it is laser cut, which tends to result in a stiff tape edge. As a result, the overlying vaginal mucosa is constantly traumatized, much more than it would be with use of mechanically cut tape." (Neuman M. J Minimally Invasive Gynec. 2011). However, there is no clinical data to support the theory, it is mere guesswork. In another study comparing Lynx to TVT, the authors found an increased rate of vaginal mesh exposures with Lynx (4% with Lynx vs. 0% with TVT) and wondered if "the heat sealed edges in the Lynx system increased its resistance to deformation, thus increasing the risk of erosion." (Agarwala. UroToday Int. J. 2008). It was suggested "the open weave Prolene [TVT] mesh also has unique biomechanical properties with low stiffness and low resistance to deformation, which may be the reason for its low risk of erosion." Again, there is no clinical data to support a finding that laser cut mesh had a lower rate of complications and patient satisfaction rates were similar both meshes.

I have also seen a company document suggesting that laser cut TVTTM mesh is 3 times stiffer than mechanically cut mesh when subjected to benchtop

testing under strain. The suggestion is that stiffer mesh causes an increase in potential complications like mesh exposure and pain. I have not seen a difference when using mechanically cut versus laser cut mesh in complication rates in the literature. I do not rely on internal company emails to guide my evidence-based clinical decisions. Plaintiffs' experts' opinions about a possible causal link between mechanically cut or laser cut causing complications are scientifically unreliable. Detailed clinical data from implants using both the mechanical and laser cut meshes provides substantial opportunity to assess for any difference in outcomes. None have been observed. These theories have not been substantiated in the context of the TVT sling by reliable data. And thus, any claim that such a warning is needed in the TVT IFU is without merit as this is not a risk.

Mesh alternatives – Ultrapro, Vypro, PVDF, Dynamesh

Some of plaintiffs' experts have speculated that the use of a partially absorbable mesh, such as Ultrapro or Vypro would be a safer alternative material than the TVT mesh for treating stress urinary incontinence. The problems with the Okulu (2013) include that it was not a well-powered study and did not directly compare the hand-made (mechanically cut) Ultrapro pubovaginal sling to TVT or TVT-O. These claims are without reliable

scientific support. Among all the mid-urethral slings, there is more data and the longest follow up for Ethicon's TVT sling. There is no credible evidence that a larger pore mesh, such as the Ultrapro mesh used for prolapse repair, would be a superior material. There is only 1 published study that has even evaluated the use of Ultrapro mesh for mid-urethral sling. This study involved 144 women who were implanted with either a combination absorbable/non-absorbable mesh (Group 1), Ultrapro mesh (Group 2) or Prolene light-weight mesh (Group 3). There was no conformity to the size of the mesh implant for each participant. The sling technique in this study consisted of mesh was attached to 2 polypropylene sutures that were passed through the retropubic space and tied down to the rectus fascia. Thus, it was not in the design of the TVT but was more similar to the technique used for pubovaginal slings. The study claims that postoperative complications were lowest in the Ultrapro group. However, review of the data indicates that there were 2 cases of mesh erosion into the vagina and 1 case of urethral erosion in Groups 1 and 3 whereas there was 1 vaginal erosion in Group 2. Due to the variation in size of the mesh, the and the deviation to the sling technique used, no weight can be attached to these small study numbers. Moreover, both Cochrane Reviews has found that monofilament type 1 mesh is the most biocompatible. (Ogah, 2011; Ford, 2015) TVT has also been studied in several long term

trials such that useful and informative long term data are available. So much so that a systematic review and metaanalysis of it has been done as earlier referenced demonstrating TVT's low long term complication rates based on data in 1,000s of patients. (Tommaselli, 2015) The same cannot be said for larger meshes in the MUS application. Thus this theory has not been substantiated in the context of the TVT sling by reliable data, and any claim that such a warning is needed in the TVT IFU is without merit as this is not a risk.

Adverse Tissue Response / Chronic Inflammation / Infection

Plaintiffs' experts' claim that inflammation occurs complication of the TVT sling procedure. However, inflammation and foreign body reactions are not complications. There are part of the natural wound healing process. Clinical studies have shown ideal tissue reaction with TVT (Falconer C. Int Urogyn J 2001). All surgeries have risks of infection and surgeons must counsel individual patients when weighing the risks and benefits of surgery. The peer-reviewed clinical literature regarding the infection rate of TVT mesh is very low. In fact wound complications with TVT are less than that with non mesh repairs like Burch and the pubovaginal sling. (Schimpf, 2014). Thus this theory has not been substantiated in the context of the TVT sling by

reliable data, and any claim that such a warning is needed in the TVT IFU is without merit.

Cytoxicity, Cancer/Sarcoma

The potential cytotoxicity of polypropylene mesh has also been raised as a potential safety concern, however there is no scientific data to support this claim. The in vitro testing accompanying the 510K FDA submission demonstrated some evidence of cytotoxicity. However, no in vivo testing raised clinical concerns. If an implant was in fact cytotoxic, it would lead to a consistent adverse host response. This would include tissue necrosis, extensive inflammation, and rejection. Despite the fact that fibrotic host responses are occasionally observed, the majority of implanted women (at least 97%) demonstrate no adverse sequelae from the mesh almost 10 years post implant. Furthermore, the suggestion in a material safety data sheet (MSDS) that polypropylene discs implanted in rats induced sarcomas at the site of implantation cannot and has not been extrapolated to humans. There is no clinical evidence supporting the plaintiffs' theory that Prolene mesh is cytotoxic and subsequently causes cancer. Further, the reliable data do not show a risk of sarcoma, cancer or incompatibility with TVT. (Moalli P., Nager C. Int Urogyn J 2014; King A, Goldman H. Curr Urol Rep 2014;

Linder BJ. Int Urogyn J 2016; AUGS/SUFU FAQs for Providers 2014). Thus this theory has not been substantiated in the context of the TVT sling by reliable data, and any claim that such a warning is needed in the TVT IFU is without merit.

Degradation

Another claim that has been made is that polypropylene mesh degrades over time and this degradation contributes to an adverse host response. Although there were reported surface cracking on SEM in a minority of samples in a small study, there was a lack of finding with regard to the hypotheses stated such as failure to demonstrate oxidation and there was a significant flaw in not having a control group. (Clave, 2010). This study cannot demonstrate degradation. The authors themselves stated that none of the hypotheses concerning degradation of polypropylene, "particularly direct oxidation, could be confirmed in this study." Another study of 24 women undergoing partial sling excision in which the mesh was not exposed revealed no evidence of graft degradation. The polypropylene mesh explants were characterized by the greatest number of infiltrating fibroblasts, a favorable histologic finding that confirms healthy tissue ingrowth (Woodruff, 2008).

There is no peer-reviewed clinical literature, including randomized controlled trials, that supports the theory that TVT degrades, loses particles, ropes, frays or curls in women overtime. There is also no evidence that supports there are clinically significant risks of degradation. I am not aware of any peer-reviewed published literature that shows specific risks or complications associated with theoretical degradation nor am I aware of any professional organizations or content experts who have expressed a concern with degradation associated with TVT or TVT-O. Plaintiffs' experts rely on clinical studies like Clave's study to suggest degradation occurs when TVT are flawed and do not confirm in vivo degradation.

Regardless of the debate about degradation, there is no level 1 evidence supporting any clinical significance to alleged degradation, or complications that arise due to degradation. Further, as the above referenced studies reflect, mesh material that has been exposed in the vagina could have different properties under a microscope than meshes that have been incorporated into host tissue. The long term data illustrates the proven efficacy of mid-urethral slings over a prolonged post-implant period, supporting that there is significant clinical evidence that the sling material remains fully functional. Thus this theory has not been substantiated in the context of the TVT sling by

reliable data, and any claim that such a warning is needed in the TVT IFU is without merit.

V. CONCLUSION

As the population grows the prevalence of stress urinary incontinence will continue to increase. It is imperative that as physicians we have an effective safe treatment option to cure stress urinary incontinence. Stress urinary incontinence can diminish the quality of life for the women experiencing the problem. The TVT sling was developed to provide a minimally a base of cure for a common problem. The alternative treatments, both surgical and nonsurgical, up to the point of the development of the TVT were ineffective or significantly invasive. The TVT sling provides a minimally invasive option for patients that allows them to return to their normal activities of daily living, work, and exercise with minimal disruption.

The TVT sling has been studied extensively. The safety and efficacy has been proven in long term studies in multiple prospective studies and metaanalysis.

The minimally invasive nature of the procedure allows this to be an effective option for multiple women. The procedure has been studied in all types of women with all types of comorbidities and has been proven safe. The TVT

sling has been proven effective safe in patients who have pure stress incontinence as well as mixed stress urinary incontinence. TVT also has been proven as the most effective treatment option for intrinsic sphincteric deficiency with urethral hypermobility.

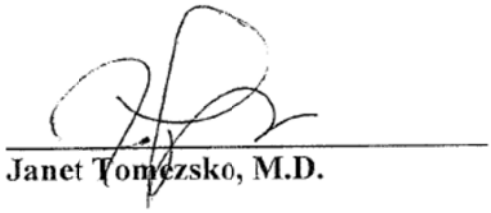
The procedure has been proven safe with very low rates of intraoperative complications such as bleeding or injury to surrounding organs such as the bladder or bowel. Postoperative complications such as urinary retention, urinary tract infections, hematoma, surgical infection, pain, or dyspareunia. The rates of these complications have been proven less than the alternative surgeries (pubovaginal slings, Burch procedures) through multiple prospective studies, controlled studies, systemic reviews as well as meta-analysis.

The major national Society's including AUGS, AUA, and SUFU have all published position papers that support the use of the TVT sling for the surgical correction of stress urinary incontinence. They support the safety and efficacy of the procedure. They support the use of the polypropylene mesh as an effective treatment for stress urinary incontinence. The FDA also has published their support of the safety of the synthetic made urethral sling.

Through the studies described above the safety of the synthetic mesh has also been well proven. The mesh complication rate is overall less than 2%. The morbidity associated with the permanent mesh has been proven very low in multiple studies as referenced above. The alternative surgeries such as pubovaginal sling and Burch procedure can also result in significant morbidity and complications with their materials and sutures. Reoperations for these procedures can be quite extensive.

At the beginning of my training as a specialist in female pelvic medicine and reconstructive surgery the TVT sling was not yet available. I had the opportunity to perform the more invasive Burch procedure as well as pubovaginal slings and the alternative needle suspensions. The development of the TVT sling revolutionized our practice and our ability to cure our patients of debilitating stress urinary incontinence. I am in full agreement with our national societies and support the use of the TVT sling. The polypropylene mesh is currently the standard of care for the surgical treatment of stress urinary incontinence. I agree the polypropylene mash is safe, effective and provides long-term symptom relief for patients. The procedure is surgically a sound procedure that can be taught consistently and performed consistently amongst surgeons. The minimally invasive nature of the

procedure allows millions of women to regain a normal lifestyle despite having developed the debilitating issue of stress urinary incontinence. I will continue to offer the TVT midurethral sling to my patients. I will continue to educate fellows and residents in the use of the mid urethral sling procedure as an important surgical treatment for stress urinary incontinence. My clinical experience with the TVT mid urethral sling over the past 15 years has been consistent with the solid clinical data. I can without hesitation say the procedure is safe, effective, and durable and an important treatment option for millions of women.



Janet Tomezsko, M.D.